Local Biologies in the Age of Precision Medicine

Margaret Lock, PhD OC
The Marjorie Bronfman Professor Emerita
Department of Social Studies of Medicine
Department of Anthropology
McGill University

I think it's safe to say we will have individualized, preventive medical care based on our own predicted risk of disease as assessed by looking at our DNA. By then each of us will have had our genomes sequenced because it will cost less than $100 to do that. And this information will be part of our medical record. Because we will still get sick, we'll still need drugs, but these will be tailored to our individual needs. They'll be based on a new breed of designer drugs with very high efficacy and very low toxicity, many of them predicted by computer models.

Francis Collins
Time Magazine, February 17 2003

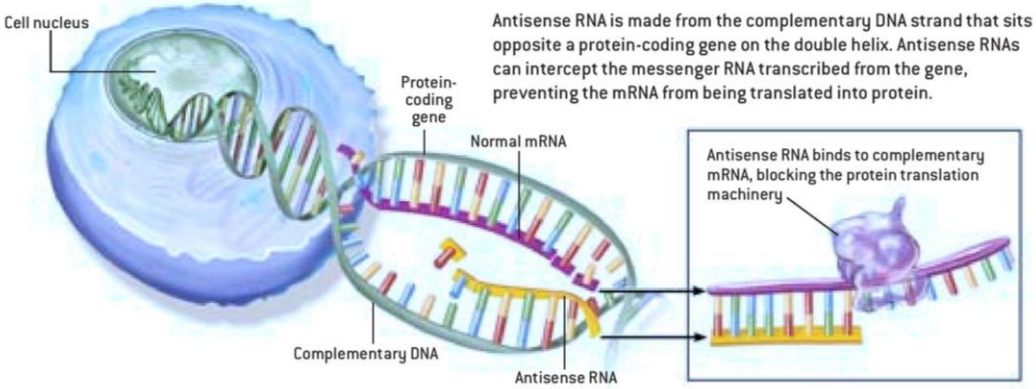
1. Humans have merely 20,000 genes, maybe a few thousand more
2. Much of our DNA is shared in common with living organisms of all kinds
3. Closely related species may have different genome sizes, and many plants have genomes much longer than that of the human genome
4. Very large segments of the human genome are comprised of what was originally termed 'junk' and shortly thereafter renamed 'dark matter.'

…new evidence…contradicts conventional notions that genes…are the sole mainspring of heredity and the complete blueprint for all life. Much as dark matter influences the fate of galaxies, dark parts of the genome exert control over the development and the distinctive traits of all organisms, from bacteria to humans…some scientists now suspect that much of what makes one person, and one species, different from the next are variations in the gems hidden within our 'junk' DNA.

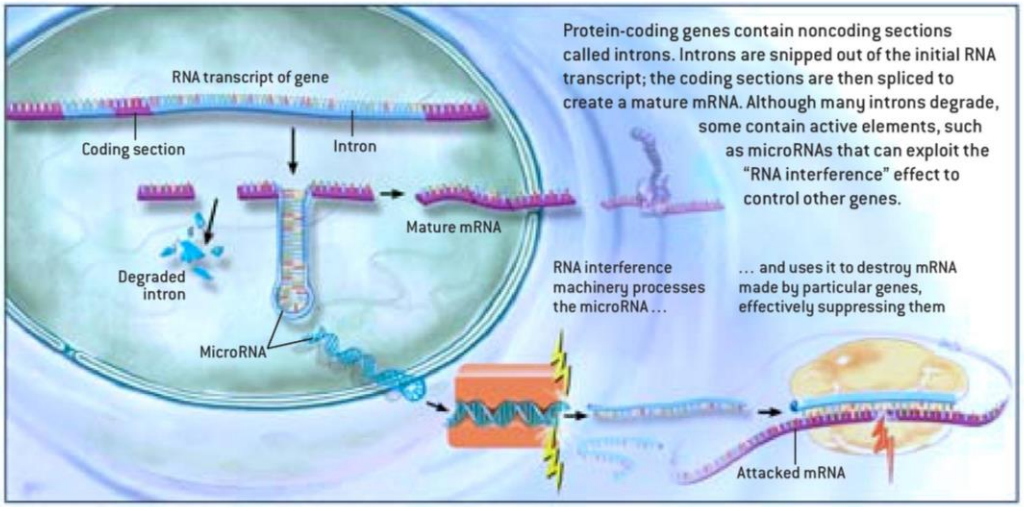
Wayt Gibbs, 2003
Scientific American 289:47-53

A BESTIARY OF UNCONVENTIONAL GENES

GENES, according to conventional wisdom, are those sections of the DNA that encode functional proteins. Such sequences make up only about 2 percent of the human genome, however. The rest of the human genome is filled with DNA that is "noncoding"—but not useless. Scientists are discovering many noncoding genes that give rise to surprisingly active RNAs, including varieties that can silence or regulate conventional genes.

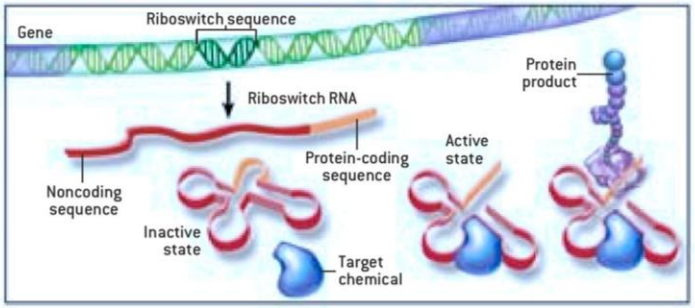


Antisense RNA is made from the complementary DNA strand that sits opposite a protein-coding gene on the double helix. Antisense RNAs can intercept the messenger RNA transcribed from the gene, preventing the mRNA from being translated into protein.



Protein-coding genes contain noncoding sections called introns. Introns are snipped out of the initial RNA transcript; the coding sections are then spliced to create a mature mRNA. Although many introns degrade, some contain active elements, such as microRNAs that can exploit the "RNA interference" effect to control other genes.

Riboswitches are a newly discovered form of RNA that act as precision genetic switches. Produced in many cases from noncoding DNA between known genes, a riboswitch folds into a complex shape. One part of the folded RNA can bind to a specific target protein or chemical. Another part contains the RNA code for a protein product. The riboswitch turns "on" and produces the protein it encodes only when in the presence of its target.



- Human variation is more subtle than had heretofore been assumed, and a great deal more remains beyond our understanding. Most of this variation is inconsequential; however, a considerable amount has significance for human health, disease susceptibility, and for precision medicine.

- Signals that affect the activity of DNA, producing both similarities and difference among genomes, arise largely in the intra-cellular environment of the organism, many of these signals are in turn responses to input from environments external to the cell and to the organism – an entanglement of gene/environment interaction takes place ceaselessly from the time of conception.

- But, equally important, the genome of the conceptus on which environmental effects impinge is always already a product of the enduring effects of evolutionary, historical, cultural, and stochastic variables to which the DNA of previous generations have been exposed over eons of time. In each individual, then, genomic difference and similarities arise from two sources – DNA contributed by each parent to form the genome of the embryo, and the effects on that genome made by environmental signals from the moment of conception.

we cannot factor a complex social situation into so much biology on one side, and so much culture on the other. We must seek to understand the emergent and irreducible properties arising from an inextricable interpenetration of genes and environment.

Stephen Jay Gould,

An Urchin in the Storm, 1987, p. 153

- All mammals have an ApoE gene for lipid transport and cholesterol metabolism.
- Three most common alleles are present in the following percentages in so-called Caucasian populations:

ApoE ε2 (7-8%)
ApoE ε3 (77-78%)
ApoE ε4 (14-16%)

- The presence of one ApoE ε4 allele accelerates the age of onset of AD by about 3-4 years, for carriers of 2 ApoE ε4 alleles the age of onset may be 8-10 years earlier than non carriers.
- Research has shown that approximately 50% of individuals who are either homozygous or heterozygous for ApoEe4 are never diagnosed with AD.

- ApoE ε2 alleles appear to be protective.

- Finch, C.E. and R. M. Sapolsky, 1999 The Evolution of Alzheimer's Disease, the Reproductive Schedule and apoE isoforms, *Neurobiology of Aging* 20:407-28

- Christian R.A. et al. 2007 Better Memory and Neural Efficiency in Young Apolipoprotein E e4 Carriers, *Cerebral Cortex* 17:1934-1947

- Corbo, R.M. and R. Scacchi 1999 Apolipoprotein E (APOE) Allele Distribution in the World: Is APOEe4 a "Thrifty Allele?" *Annals of Human Genetics* 63:301-310

International Studies in Dementia With Particular Emphasis on Populations of African Origin

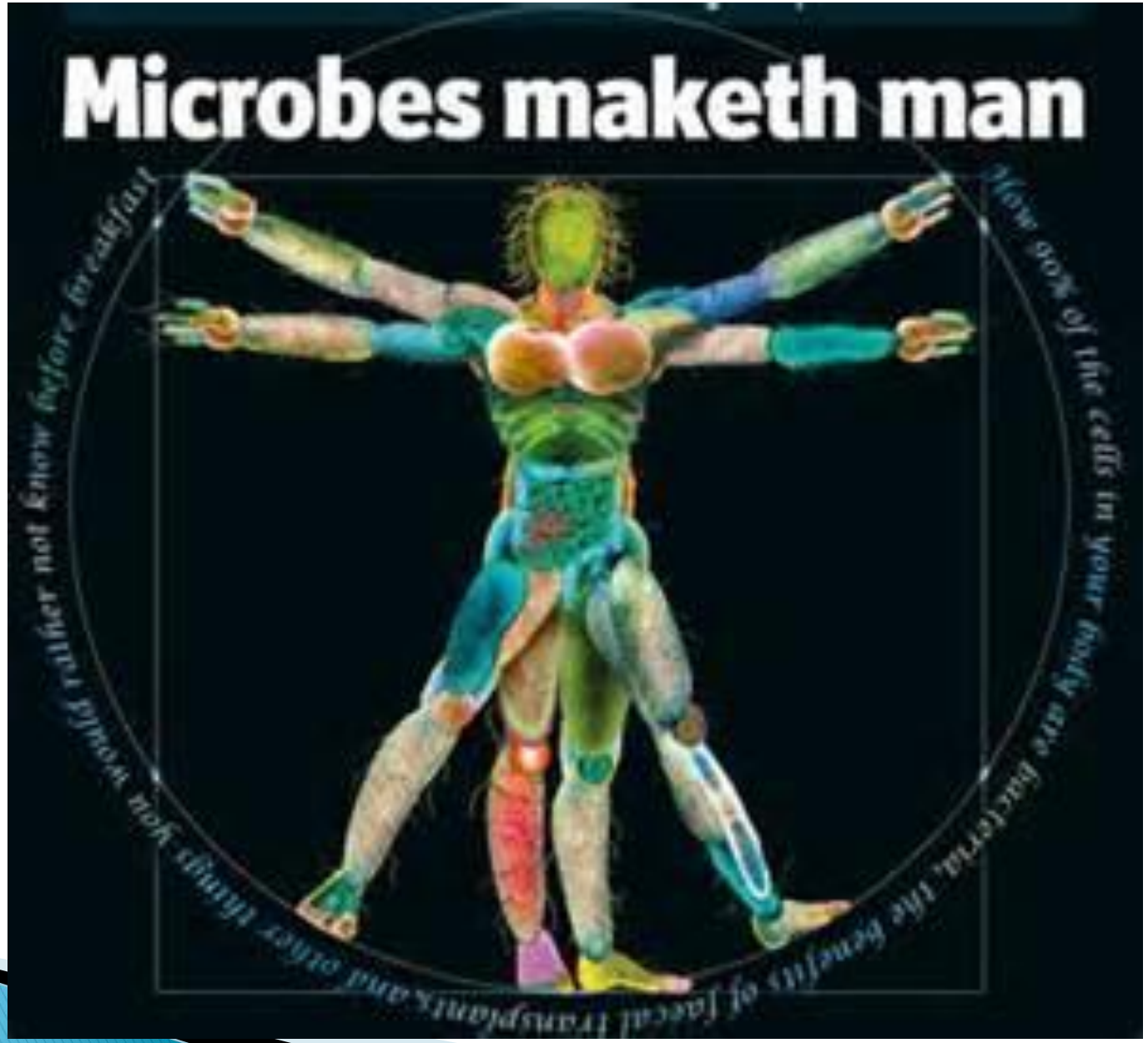
Hendrie, Hugh C. MB, ChB, DSc et al.2006 Alzheimer Disease & Associated Disorders: July/September 2006 - Volume 20 – pp S42-S46

- Incidence of Alzheimer's disease and dementia among Yoruba are less than half that of African Americans
- Frequency of ApoE ε4 more or less the same in both populations
- Yoruba have a lower incidence of vascular disease and vascular risk factors, including hypertension than do African Americans.
- Yoruba cholesterol and lipid levels much lower

- Marasmus: a wasting disease caused by profound generalized malnutrition. “Metabolically thrifty”
- Kwashiorkor: malnutrition caused by severe protein-energy malnutrition causing odema and anorexia among other severe symptoms. “Metabolically profligate”

Forrester, Terrence E., et al. 2012. Prenatal factors contribute to the emergence of kwashiorkor or marasmus in severe undernutrition: evidence for the predictive adaptation model. Plos One 7(4): e35907. doi:10.1371

Gluckman, Peter, and Mark Hanson. 2008 Mismatch: the lifestyle diseases timebomb. Oxford: Oxford University Press.


Microbes maketh man
Now 90% of the cells in your body are bacterial. The benefits of faecal transplants and other things you would rather not know before breakfast

…life might not be law-like in the Enlightenment sense, or even that we may not know when we have found such laws.

Kenneth Weiss and AnnBuchanan

Genetics 2011, 188: 761-771.